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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,590	HUSE, WILLIAM D.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 80-92 is/are pending in the application.

4a) Of the above claim(s) 80-84 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 85-92 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/11/2001.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 80-92 are pending.

2. Applicant's election with traverse of Group II, claims 85-92 in the Paper filed 2/11/2004 is acknowledged. The traversal is on the grounds that the examination of groups I and II together would not be an undue burden on the examiner and a search of the method claims of Group II would reveal relevant art to the grafted antibody of Group I. This is not found persuasive because of the reasons set forth in paper mailed 8/11/2003. Inventions I and II are related as process of making and product made. The inventions can be shown to be distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make a materially different product or (2) that the product as claimed can be made by another materially different process (MPEP § 806.05(f)). In the instant case, the product of Group I can be made by a materially different process such as "framework exchange". Because the inventions are distinct for the reasons given above and the search for Group II is not required for Group I and Groups I and II have acquired a separate status in the art as shown by their different classification and divergent subject matter, restriction for examination purposes as indicated is proper.

As to the question of burden of search, the antibody of Group I is classified in class 424, subclass 133.1 and the method of Group II is classified in class 435, subclass 69.6. The divergent classification of subject matter is merely one indication of

the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and different patentability issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made FINAL.

Applicant's request for a "second-eye review" under the Restriction Practice Action Plan is acknowledged, however, the "second-eye review" as currently implemented only applies to subsequent restriction requirements and no subsequent restriction requirement has been set forth in the instant application.

3. Claims 80-84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

4. Claims 85-92 are under examination.

Specification

5. The abstract of the disclosure is objected to because the abstract exceeds the maximum length. The abstract should be within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited.

Correction is required. See MPEP § 608.01(b).

6. The disclosure is objected to because of the following informalities:

a. Table 8 is missing and Tables 8-10 are not consecutive. For example, Table 10 is disclosed on page 87 and Table 9 is disclosed on page 91.

b. There is a Table 10 on page 87 and a second Table 10 on page 97.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 85-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 85-92 are indefinite for reciting "enhanced antibody" and "functional fragments thereof" because their characteristics are not known. This language is vague and indefinite since it encompasses many different amino acid (and nucleic acid sequences) as well as many different forms and modifications and it is not clear from the disclosure which particular "enhanced" or "function" attribute is being referred to. There is insufficient information and guidance concerning the metes and bounds of said "enhanced" and "function" as it relates to the structure/function of the antibodies and nucleic acids encoding the antibodies. The metes and bounds of said "enhanced antibody" and "functional fragments thereof" have not been clearly defined in the

specification as filed. Does the term "enhanced" mean an increased association rate constant or association constant or is some other meaning contemplated by the term?

b. Claims 85-92 are indefinite in the recitation of "modifying" in claim 85 because the claims fail to state the function, which is to be achieved. The term "modifying" is relative in nature, which renders the claims indefinite. The term "modifying" is not defined by the claims; the specification does not provide a standard for ascertaining the direction, requisite degree or endpoint, and one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention. Does the term "modifying" mean that the parent antibody is mutated or digested with an enzyme or aglycosylated or labeled or is some other meaning contemplated by the term "modifying"?

c. Claim 92 is indefinite for reciting "grafted antibody" because the metes and bounds of said phrase or the defining structural features are unclear. "Grafted antibody" is a broad phrase that encompasses any number of recombinant forms of antibodies and applicant has not provided sufficient direction to define said "grafted antibody" forms. Amending the claims to recite "CDR grafted", would obviate this rejection, provided no new matter is added.

d. Claim 85 recites the limitation "the rate". There is insufficient antecedent basis for this limitation in the claim. Claim 85 recites "association rate constant" and association rate" and it is unclear if the "association rate constant" and "association rate" are intended to be the same or if "association rate" is meant to be the association

constant. Does the phrase "association rate" mean the association rate constant (k_{on}) or the association constant (K_a)?

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 85-87, 90 and 91 are rejected under 35 U.S.C. 102(b) as being anticipated by Schier et al (Journal of Molecular Biology, 263:551-567, 1996, Ids filed 10/11/01).

The claims are interpreted as being drawn to a method of producing an antibody or functional fragment thereof having an increased association constant or affinity to an antigen comprising one or more amino acid substitutions in one or more of the CDRs in one or more of the variable regions and measuring the association rate constant of the variant antibodies, wherein a variant or functional fragment thereof has an association constant or affinity that is 4-fold higher compared to the parent antibody. The method further comprises isolating the antibody having an increased association constant and

said antibody has an association rate constant (k_{on}) that is 6.8 X 10^5 M^{-1} sec^{-1} or higher and an association constant (K_a) that is 2.0 X 10^9 M^{-1} or higher.

Schier et al teach a method of producing a higher affinity anti-c-erbB-2 single-chain Fv comprising sequentially mutating (i.e., modifying) CDR3 of the variable light chain and variable heavy chain, obtaining mutated antibodies by selection and purification, determining the association rate constants using a BIAcore biosensor and the mutated antibodies had an affinity (i.e., association constant) to antigen that was typically 4-fold greater compared to the affinity of the wild-type antibody or parental antibody) (see page 553-554 and 556 and Tables 2 and 4). Further, certain mutant VL, and VL-VH CDR3 mutant antibodies had association rate constants (k_{on}) greater than 6.8 X 10^5 M^{-1} sec^{-1} (see tables 2-4) and certain mutant VL-VH mutant antibodies had an association constant (K_a) greater than 2.0 X 10^9 M^{-1}. It is inherent to one skilled in the relevant art that the dissociation constant (K_d) presented in Tables 2-4 is the mathematical inverse of the K_a. Thus, $K_a = 1/ K_d$; meaning that the wild-type antibody (C6.5) in Table 4 has a K_a of 6.25 X10^7 M^{-1} and mutated VL-VH antibodies having a K_d value less than 4.7 have a K_a greater than 2.0 X 10^9 M^{-1} since the K_d value of 4.7 equates to a K_a value of 2.1 X 10^9 M^{-1}. Therefore, Schier et al anticipate the claims.

11. Claims 85-89 and 92 are rejected under 35 U.S.C. 102(b) as being anticipated by Deng et al (Canadian Patent, 2,125,240 A1, published 12/7/1995).

Claims 85-87 and their interpretation have been described supra.

Claims 88-89 and 92 further limit parent claim 85 by reciting wherein one or more amino acid substitutions are in one or more framework regions and wherein one or more amino acid substitutions are in one or more CDRs and one or more framework regions. Claim 92 further limits parent claim 85 by reciting that the enhanced antibody is a grafted antibody or functional fragment thereof.

Deng et al teach methods for antibody affinity maturation and humanization by CDR grafting and randomization of the framework residues and the CDRs and frameworks can be randomized (see pages 12-13). Deng et al teach a method for affinity maturation of a single-chain antibody by randomizing the CDRs of the variable heavy chain such that amino acid substitutions are introduced at a level that approximates that resulting form somatic hypermutation during the affinity maturation stage of the immune response (see page 12 and Examples 1-2). The randomized variable heavy chain antibody is selected by phage display and the antibodies were purified by affinity chromatography and the kinetics of binding to antigen were measured using a BIAcore biosensor (see example 1). Deng et al teach that the association rate of the randomized variable heavy chain antibodies was greater than 4-fold compared to the association rate of the wild-type antibody (see Table 3). Deng et al also teach a two-stage method for in vitro affinity maturation of a single-chain antibody in which a VH mutant with improved affinity is isolated from a heavy chain CDR-randomized library as described above and in the second stage a light chain CDR-randomized product is inserted into the vector containing the affinity matured heavy chain (see example 2 and Figure 7). Deng et al also teach CDR grafting wherein mouse CDRs are grafted onto

human frameworks and Deng teaches a method of humanizing a mouse antibody by randomizing the limited number of residues which differ in the mouse and human frameworks in conjunction with phage display (see pages 12-13 and example 3).

12. Claims 85-91 are rejected under 35 U.S.C. 102(e) as being anticipated by Marks et al (U.S. Patent 5,977,322, filed 1996).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims and their interpretation have been described supra.

Marks et al teach a method of producing a mutant single-chain Fv (scFv) comprising chain shuffling wherein either the VH or VL gene from a binding scFv is replaced with a repertoire of nonimmune VH or VL and such gene repertoires contain numerous variable genes derived from the same germline gene, but with point mutations (see column 13 and column 16, lines 21-25). Further, since the VH or VL chain of the parent antibody is substituted with a complete VH or VL chain, which contains CDRs and frameworks, at least one or more amino acid substitutions are in one or more of the CDRs and one or more of the frameworks. Marks et al teach phage display for the selection of the mutant scFvs and purification of the mutant scFvs (see

columns 13-14). Marks et al teach measuring the association rate constant (k_{on}) of the mutant scFvs measured using a BIAcore biosensor (see column 14) and the association constant (K_a) or affinity of the mutant scFv to an antigen is 4-fold higher compared to the K_a of the parent antibody (see Table 3). Marks et al teach mutant scFvs that have k_{on} that is greater than 6.8×10^5 M^{-1} sec^{-1} (see Table 3). Marks et al teach CDR randomization using NNS nucleotides (i.e., codon-based mutagenesis) for creating higher affinity scFv (see column 17, lines 23-26, column 18, column 21, lines 16-30). Marks et al teach that the CDRs can be randomized sequentially, in parallel, and mutations can be combined to achieve an additive effect on affinity (see column 21, lines 1-7). Marks et al teach a dimeric scFv having a dissociation constant (K_d) of 4.0×10^{-10} M (see Table 5 and columns 75-76). It is inherent to one skilled in the relevant art that the K_a is the mathematical inverse of the K_d and both are a measure of affinity. Thus, $K_a = 1/K_d$; meaning that the K_d value of 4.0×10^{-10} M as indicated in Table 5 is equivalent to a K_a value of 2.5×10^9 $^{-}$M, which is greater than 2.0×10^9 $^{-}$M and meets the limitation of instant claim 91. Thus, Marks et al anticipate the claims.

13. Claims 85-87 are rejected under 35 U.S.C. 102(b) as being anticipated by Yelton et al (The Journal of Immunology, 155:1994-2004, 1995).

The claims and their interpretation have been described supra.

Yelton et al tech a method for affinity maturation of the BR96 anti-carcinoma antibody by codon-based mutagenesis. Yelton et al teach that the method comprises randomizing or mutating CDRs by codon-based mutagenesis, screening the library for

higher affinity variants (i.e., obtaining and isolating) and measuring the association rate constant (see page 1997-2000 and Table II). Yelton et al teach that the affinity (i.e., association constant) of the variant antibodies is 4-fold greater compared to the affinity of the parent antibody (see page 2000, left column and K_d values in Table II). It is inherent to one skilled in the relevant art that the association constant K_a is the mathematical inverse of the K_d and both are a measure of affinity.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. Claims 85-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schier et al (Journal of Molecular Biology, 263:551-567, 1996, Ids filed 10/11/01) as

applied to claims 85-89, 90 and 91 above, and further in view of Foote et al (Journal of Molecular Biology, 224:487-499, 1992).

The claims are interpreted as being drawn to a method of producing a CDR grafted antibody or functional fragment thereof having an increased association constant or affinity to an antigen comprising one or more amino acid substitutions in one or more of the CDRs and/or in one or more framework regions in one or more of the variable regions and measuring the association rate constant of the variant antibodies, wherein a variant or functional fragment thereof has an association constant or affinity that is 4-fold higher compared to the parent antibody. The method further comprises isolating the antibody having an increased association constant or affinity and said antibody has an association rate constant (k_{on}) that is 6.8 X 10^5 M^{-1} sec^{-1} or higher and an association constant (K_a) that is 2.0 X 10^9 M^{-1} or higher.

Schier et al teach a method of randomizing or mutating the CDR3 regions of the variable light and heavy chains that produced picomolar affinity. The method of Schier et al comprises sequentially mutating (i.e., modifying) CDR3 of the variable light chain and variable heavy chain, obtaining mutated antibodies by selection and purification, determining the association rate constants using a BIAcore biosensor and the mutated antibodies had an affinity (i.e., association constant) to antigen that was typically 4-fold greater compared to the affinity of the wild-type antibody or parental antibody) (see page 553-554 and 556 and Tables 2 and 4). Further, Schier et al teach that certain mutant VL, and VL-VH CDR3 mutant antibodies had association rate constants (k_{on}) greater than 6.8 X 10^5 M^{-1} sec^{-1} (see tables 2-4) and certain mutant VL-VH mutant

antibodies had an association constant (K_a) greater than 2.0 X 10^9 M^{-1}. It is inherent to one skilled in the relevant art that the dissociation constant (K_d) presented in Tables 2-4 is the mathematical inverse of the K_a. Thus, $K_a = 1/ K_d$; meaning that the wild-type antibody (C6.5) in Table 4 has a K_a of 6.25 X10^7 M^{-1} and mutated VL-VH antibodies having a K_d value less than 4.7 have a K_a greater than 2.0 X 10^9 M^{-1} since the K_d value of 4.7 equates to a K_a value of 2.1 X 10^9 M^{-1}. Schier et al also teach that higher affinity antibodies should make possible selective delivery to tumor antigens (see page 552). Schier et al do not specifically teach a CDR grafted antibody or substitutions in the framework regions. These deficiencies are made up for in the teachings of Foote et al.

Foote et al teach a method of producing a humanized or reshaped (i.e., CDR grafted) antibody wherein the reshaped antibody comprises CDRs from a mouse antibody D1.3 and the framework regions of human Vκ(I) family and the myeloma protein NEW (see page 488, left column). Foote et al teach that reshaped antibodies have shown clinical success and substitutions in the framework regions of CDR grafted antibodies may exert a determining influence on the conformation of the CDRs and thus, are important for antibody specificity and affinity (see pages 487-488). Foote et al teach that certain framework mutations contributed to enhanced affinity and framework residues are located in the Vernier zone have been shown to be important in restoring the affinity in CDR grafted antibodies and alterations at these points may have some role in affinity maturation (see page 497, left and right columns).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method of combining antibody

humanization and affinity maturation of an antibody by randomization in the CDRs and framework residues of a CDR grafted antibody for affinity maturation since certain framework residues support CDR structure and antibody affinity.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a method of combining antibody humanization and affinity maturation of an antibody by randomization in the CDRs and framework residues of a CDR grafted antibody for affinity maturation since certain framework residues support CDR structure and antibody affinity in view of Schier et al and Foote et al because Schier et al teach a method of randomizing or mutating the CDR3 regions of the variable light and heavy chains that produced picomolar affinity and Foote et al teach that substitutions in the framework regions of CDR grafted antibodies may exert a determining influence on the conformation of the CDRs and thus, are important for antibody specificity and affinity and framework mutations located in the Vernier zone contributed to enhanced affinity and alterations at these residues may have some role in affinity maturation. Therefore, it would have been obvious to concurrently optimize CDR and framework residues of a CDR grafted antibody because certain framework and CDR residues are spatially close and likely to interact with one another and this approach takes into account the beneficial combinations of CDR and framework residues. Thus, it would have been obvious to one skilled in the art to produce a method of combining antibody humanization and affinity maturation of an antibody by randomization in the CDRs and framework residues of a CDR grafted

antibody for affinity maturation since certain framework residues support CDR structure and antibody affinity in view of Schier et al and Foote et al.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at (571) 272-0827 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER